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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,587	07/23/2003	Henry Li	016556-003210US	4103

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EXAMINER
SHIBUYA, MARK LANCE

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/628,587	LI ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-15,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22 are pending. Claims 1-15, 21 and 22 are withdrawn. Claims 16-20 are examined.

Election/Restrictions

2. Applicant's election with traverse of Group III, claims 16-20, and election of the species of hairpin linker of the sequence as specified, a Pol III promoter that is U6 snRNA promoter, and the tetO operator, in the reply filed on 3/22/2006, is acknowledged. The traversal of the restriction of Invention is on the ground(s) that the library of Group II is a random library that *can* be physically distinguished from a non-random library. This is not found persuasive because as applicant notes, there is no physical differences between the members of the library based on randomness. A few/plurality of members of the claimed DNA expression of cassettes, which would read on the claimed random library, could be synthesized by methods other than that of the Invention of Group II; particularly if the sequences of the "random" members were known.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-16, 21 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/22/2006.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

5. This application, filed 7/23/2003, claims benefit of 60/399,040, filed 7/24/2002.

Information Disclosure Statement

6. The information disclosure statement (IDS), submitted on 2/22/2005, has been considered by the examiner.

Specification

7. Applicants disclose nucleotide sequences in the text of the specification (see, e.g., p. 17, lines 5, 14; p. 19, line 2; p. 19, line 2; p. 51, line 17) and the drawings, that must be identified by a SEQ ID number, pursuant to 37 CFR 1.821(d), which requires that where the description or claims of a patent application discuss a sequence listing that is set forth in the 'Sequence Listing' in accordance with paragraph (c) of this

section, reference must be made to the sequence by use of the assigned identifier, in the drawings or the "Brief Description of the Drawings", in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. The examiner respectfully requests applicant's assistance to insure that all sequences within the sequence rules, which are to be found in the specification, comply with the sequence rules.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Lorens, US 2004/0005593 A1**, (6/6/2002; IDS filed 2/22/2005, cite no. AC); and in view of **Gunnery et al.**, Journal of Molecular Biology, (1999 Feb 26) Vol. 286, No. 3, pp. 745-57 and **Thompson, US 6,146,886 A**.

The claims are drawn to a method for producing a library of DNA expression cassettes comprising: (a) synthesizing a plurality of partially randomized nucleic acid sequences, each having a 5' and a 3' end and comprising; a series of 1 to 23 bases linked at its 3' end to a plurality of at least four consecutive adenylyl residues linked at its 3' end to a randomized nucleic acid sequence of from 11 to 27 bases long linked at its 3' end to a polymerase primer hairpin linker having the sequence $N^1{}_nN^2{}_mN^3{}_n$, where N^3 is complementary to N^1; n is a number greater than or equal to 2; and, m is a number from 1 to 40 wherein the randomized nucleic acid sequence is different in each of the expression cassettes in the library; (b) extending each partially randomized nucleic acid sequence from the polymerase primer hairpin linker using the nucleic acid sequence 5' to the polymerase primer hairpin linkers as a template; (c) denaturing each of the extended partially randomized nucleic acid sequences; (d) annealing a 5' primer to the 5' end and a 3' primer to the 3' end of each of the denatured partially randomized nucleic acid sequences; (e) ligating each annealed partially randomized nucleic acid sequence into a separate expression vector comprising a modified pol III promoter having a TATA box, wherein the modified pol III promoter is operably linked to the extended partially randomized nucleic acid sequence, the pol III promoter being modified whereby transcription from the promoter begins at the first base of the

randomized nucleic acid sequence; and, (f) generating a complementary strand to each partially randomized nucleic acid sequence, thereby forming a complete DNA expression cassette; and variations thereof.

Lorens, US 2004/0005593 A1, throughout the publication and figures, especially Fig. 2, disclose methods for producing a library of DNA oligonucleotides cloned into a retrovirus vector, reading on expression cassettes. Lorens states:

> Random libraries of interfering RNA molecules may be constructed by synthesizing a pool of oligonucleotides comprising a restriction site, a randomized siRNA sequence, a complementarity region sequence, and a hairpin-forming linker sequence (optionally a U-turn motif, a ribozyme and/or or a two complementary sequences that form a hairpin or stem loop structure). The oligonucleotides will adopt a hairpin structure as shown in FIG. 2. This structure is a substrate for a DNA polymerase, facilitating the synthesis of a complement sequence of the randomized siRNA sequence. The hairpin structure is then denatured and hybridized to a primer at the 3' end allowing the conversion of the total sequence to double stranded DNA by a DNA polymerase. The double stranded oligonucleotides encoding a random assortment of siRNA sequences are cloned into the retroviral vector described herein to generate an siRNA-expression vector library.

Lorens, US 2004/0005593 A1, at para [0020].

Thus Lorens teaches methods of preparing DNA oligonucleotides encoding a random assortment of siRNA, reading on methods comprising: (a) synthesizing a plurality of partially randomized nucleic acid sequences, each having a 5' and a 3' end, as claimed. Lorens, at para [0020] and Figure 2, teach a restriction site (RE), reading on nucleic acid sequences comprising a series of 1 to 23 bases, which are linked at its 3' end to a randomized siRNA sequence, which is capable of RNA interference, and that has 20-25, e.g., 20, 21, 22 nucleotides, as taught by Lorens, at para [0004], which reads

on a randomized nucleic acid sequence of from 11 to 27 bases long, as in claims 16 and 17.

Lorens, at para [0020], teaches a complementarity region (CR) linked to a hairpin-forming (stem loop), which reads on linker sequences linked at its 3' end to a polymerase primer hairpin linker having the sequence $N^1{}_nN^2{}_mN^3{}_n$, where N^3 is complementary (complementarity regions) to N^1; wherein the randomized nucleic acid sequence is different in each of the expression cassettes in the library, as in the claims.

Lorens, at para [0020], teaches that the hairpin structure is then denatured and hybridized to a primer at the 3' end allowing the conversion of the total sequence to double stranded DNA by a DNA polymerase, reading on (b) extending each partially randomized nucleic acid sequence from the polymerase primer hairpin linker using the nucleic acid sequence 5' to the polymerase primer hairpin linkers as a template; (c) denaturing each of the extended partially randomized nucleic acid sequences; (d) annealing a 5' primer to the 5' end and a 3' primer to the 3' end of each of the denatured partially randomized nucleic acid sequences, as in the claims.

Lorens, at para [0020], discloses that the double stranded oligonucleotides encoding a random assortment of siRNA sequences are cloned into the retroviral vector described herein to generate an siRNA-expression vector library, which reads on (e) ligating each annealed partially randomized nucleic acid sequence into a separate expression vector, as in the claims.

Lorens, at, e.g., the Summary of the Invention (para [0005]) and Figure 2, teach expression vectors comprising a modified pol III promoter, wherein the modified pol III

promoter is operably linked to the extended partially randomized nucleic acid sequence, (f) generating a complementary strand to each partially randomized nucleic acid sequence, thereby forming a complete DNA expression cassette, as in the claims.

Lorens, at para [0013], teaches that the expression vectors may be expressed in bacterial cells, as in claim 18. Lorens, at para [0020] teach using DNA polymerase to synthesize a complementary strand to each partially randomized nucleic acid sequence as in claim 19.

Lorens, does not teach methods for producing a library of DNA expression cassettes of oligonucleotides encoding siRNA, wherein the oligonucleotides comprise a plurality of at least four consecutive adenylyl residues linked at its 3' end to the randomized nucleic acid sequence. Lorens does not teach producing a library of DNA oligonucleotides comprising a pol III promoter having a TATA box and being modified whereby transcription from the promoter begins at the first base of the randomized nucleic acid sequence.

Gunnery et al., throughout the publication and abstract, and e.g., pp. 745-46, bridging paragraph, teach that RNA polymerase III (pol III) transcription generally terminates at a run of four or more thymidine (T) residues. Gunnery et al., at p. 745, para 1, teach genes encoding the small RNAs U6 as being transcribed by type 3 pol III.

Thompson, US 6,146,886 A, throughout the patent, and at, e.g., col. 1, lines 43-col. 2, line 5, teaches type 3 pol III promoter sequences as comprising a traditional TATA box.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for producing a library of DNA expression cassettes of oligonucleotides encoding siRNA, wherein the oligonucleotides comprise a plurality of at least four consecutive adenylyl residues linked at its 3' end to the randomized nucleic acid sequence; and for producing a library of DNA oligonucleotides comprising a pol III promoter having a TATA box and being modified whereby transcription from the promoter begins at the first base of the randomized nucleic acid sequence.

One of ordinary skill in the art would have been motivated to make and use methods for producing a library of DNA expression cassettes of oligonucleotides encoding siRNA, wherein the oligonucleotides comprise a plurality of at least four consecutive adenylyl residues linked at its 3' end to the randomized nucleic acid sequence because it would be desirable to provide a termination signal after the complementary strand to the randomized sequence, in order to produce siRNA, which is required to be of defined size, as taught by Loren, and because Gunnery et al., teach that pol III transcription terminates at a run of four or more thymidine, which would result from DNA polymerase primer extension of at least four consecutive adenylyl residues, (as evidenced by **Lehninger**, Biochemistry, The Molecular Basis of Cell Structure and Function, Worth Publishers, Inc., New York, 1970, pp. 670-71, and particularly Figures 29-8 and 29-9), linked at the 3' end to the randomized sequence (and as observable upon inspection of Fig. 2 of Lorens).

One of ordinary skill in the art would have been motivated to make and use methods and for producing a library of DNA oligonucleotides comprising a pol III promoter having a TATA box, because the TATA box supports type 3 pol III transcription, as taught by Thompson, US 6,146,886 A. One of ordinary skill in the art would have been motivated to make and use methods and for producing a library of DNA oligonucleotides comprising a pol III promoter being modified whereby transcription from the promoter begins at the first base of the randomized nucleic acid sequence, in order to produce siRNA of the required sized, as taught by Loren.

One of ordinary skill in the art would have had a reasonable expectation of success in methods for producing a library of DNA expression cassettes of oligonucleotides encoding siRNA, wherein the oligonucleotides comprise a plurality of at least four consecutive adenylyl residues linked at its 3' end to the randomized nucleic acid sequence; and for producing a library of DNA oligonucleotides comprising a pol III promoter having a TATA box and being modified whereby transcription from the promoter begins at the first base of the randomized nucleic acid sequence because the molecular engineering of vector constructs to comprise defined nucleic acid sequences were well-known in the art at the time of invention, as indicated by the cited prior art.

10. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Lorens, US 2004/0005593 A1**, (6/6/2002; IDS filed 2/22/2005, cite no. AC); and in view of **Gunnery et al.**, Journal of Molecular Biology, (1999 Feb 26) Vol. 286, No. 3, pp. 745-57

and **Thompson, US 6,146,886 A**, as applied to claims 16-19 above, and further in view of **Elbashir et al.**, EMBO Journal, Dec. 3, 2001, Vol. 20, No. 23, pp. 6877-6888 and **Brummelkamp et al.**, Science, 19 April 2002, Vol. 296, pp. 550-p. 553, (IDS filed 2/22/2005, cite no. AF).

Lorens, **Gunnery et al.**, and **Thompson, US 6,146,886 A**, are relied upon, as applied to claims 16-19 above.

Lorens, Gunnery et al., and Thompson, US 6,146,886 A, do not disclose methods for producing a library of DNA expression cassettes of oligonucleotides encoding siRNA, wherein the oligonucleotides comprise a polymerase primer hairpin linker having the sequence $N^1{}_nN^2{}_mN^3{}_n$, as in claim 16, and wherein the first two nucleotides of N^2 is a sequence of two thymidyl residues.

Elbashir et al., EMBO Journal, Dec. 3, 2001, Vol. 20, No. 23, pp. 6877-6888, teach at p. 6884, siRNA oligonucleotides comprising 2 nucleotide 3' overhangs that were TT, in order to reduce the costs of synthesis.

Brummelkamp et al., Science, 19 April 2002 Vol. 296, pp. 550-p. 553, (IDS filed 2/22/2005, cite no. AF), at p. 550, para 1, Fig. 1A, and p. 551, para 4, teach the expression of siRNA from vectors wherein a 49-nucleotide precursor transcript is rapidly cleaved to siRNA, thereby indicating that the stem-loop precursor transcript is generated and cleaved in the cell, resulting in a TT nucleotide overhang, to produce functional siRNA.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for producing a library of DNA

expression cassettes of oligonucleotides encoding siRNA, wherein the oligonucleotides comprise a polymerase primer hairpin linker having the sequence $N^1{}_nN^2{}_mN^3{}_n$, as in claim 16, and wherein the first two nucleotides of N^2 is a sequence of two thymidyl residues, as in instant claim 20.

One of ordinary skill in the art would have been motivated to use methods for producing a library of DNA expression cassettes of oligonucleotides encoding siRNA, wherein the first two nucleotides of N^2 of the oligonucleotides, is a sequence of two thymidyl residues in an oligonucleotide encoding siRNA having a 2 nucleotide 3' overhang, in order to reduce the cost of synthesis, as taught by Elbashir et al.

One of ordinary skill in the art would have had a reasonable expectation of success in using methods for producing a library of DNA expression cassettes of oligonucleotides encoding siRNA, wherein the first two nucleotides of N^2 is a sequence of two thymidyl residues, because Brummelkamp et al., teach the expression of siRNA from vectors wherein the stem-loop precursor transcript is generated and cleaved in the cell, resulting in a TT nucleotide overhang, in order to produce functional siRNA.

Conclusion

11. Claims 16-20 are rejected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark L. Shibuya
Examiner
Art Unit 1639